Dear Josh —

COPY

Here is the letter.

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Editor
Scientific American
415 Madison Avenue
New York 17, New York

Sirs:

Science and the Citizen (Scientific American, August 1963, pp. 50-52) discusses the possibility that the genetic code may not be genetically determined. The evidence today is that the code has been fixed throughout most of evolution, and seems not subject to mutation. The article argues that "this may mean either that no change can produce an improvement, which seems unlikely, or that transfer RNA's can make only certain fixed associations." (Italics mine.)

I will argue that the genetic code has a special status, in the hierarchy of control, that would make it very surprising for any change to produce any viable cells at all, to say nothing of possible improvements! It is believed that the code mediates the synthesis of all protein by a uniform translation mechanism. According to our present understanding, a change in the amino-acid, RNA-string correspondence would cause a simultaneous substitution of one amino-acid for another throughout every protein in the organism, at all sites involving the base-sequence in question. The result would be a qualitative change in virtually all the significant electrical, geometric, and chemical properties of every protein molecule. We know that single gene-mutations are usually unfavorable; it is a foregone conclusion that the result here, which corresponds to that of hundreds, or perhaps tens of thousands, of simultaneous mutations would be instantly fatal to the cell strain.

When a strain survives a single mutation, it is rarely an improvement; survival is more often due to the availability of an alternative metabolic pathway around a changed mechanism. A change that affects all pathways has then almost no chance to be innocuous, and less chance to be favorable.

But I want to make it quite clear that I am suggesting something stronger than that "a favorable mutation in the coding system is very improbable". Rather I am suggesting the likelihood that "no change whatever in the coding will be viable"--that there may be no exceptions and that the matter is not even one of low probability! That is, there may be no rearrangement of the

encoding which, without a corresponding revision of all the information written on the RNA strings themselves, will allow viability.

There is an interesting parallel vis-a-vis the control mechanism of the modern digital computer. The program of a computer is a bunch of strings of digits in the machine's memory cores. The control element of a computer is the mechanism that interprets these digits to perform operations that make other changes in the contents of the memory. We know from experience that "viable mutations" in a computer program are very unusual. That is, if one changes a single digit in the program, the result is usually a complete failure. But there are situations in which the program still works approximately, and situations in which there are no apparent effects at all. I know of only one instance in which an accidental change caused a real improvement (in causing a process to converge, when the intended program would have caused instability); such events are rare enough to celebrate. This is the same general picture familiar in connection with gene-mutation.

A change in a computer program affects only a certain part of the process determined by that program. A change in the computer's control element changes the way in which all the digit codes of the program are translated into the data-processing operations performed by the machine's gates and registers. In particular, each change in the significance of any of the digits that enter the control element would change the effect of almost every section of the program. Such a "mutation" would mean that no program that once did something useful would now do anything useful, with the possible exception of trivially simple cases. This critical site corresponds rather clearly to the messenger-RNA pairing, if the program corresponds, in our metaphor, to the RNA base-sequence of the chromosome, and the remainder of the control element to the remainder of the protein-synthesis machinery.

Thus it seems quite possible that the effect of every change in the genetic code (multiple as well as single) would be a scrambling as fatal as denaturing all the cell's protein. So it remains perfectly possible that the correspondence dictated by the messenger-RNA system is as subject to genetic control as any other system. But once we deal with organisms dependent on the structure of and relations between a few protein strings, the evolution of this system must halt abruptly because all small changes become totally disastrous. Observe that a single genetic change in this system would probably change the whole system in the daughter cells, because of the changes mitochondrial protein.

Hence fixation of the code gives us no reason to postulate unknown constraints in the amino-acid;base-sequence correspondence of messenger-RNA. There may in fact be such constraints (plausible merely on grounds

of geometric--template-like--affinities), but I think the above argument is more likely to hold the answer to the universality of the code.

Sincerely,

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M.I.T.

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